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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/121,239	07/23/98	HARVEY R	GP091-02.UT

EXAMINER	
SCHMIDT, M	
ART UNIT	**PAPER NUMBER**
1635	5

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HM12/0818

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)

1- File Copy

Office Action Summary

Application No.	Applicant(s)
09/121,239	Harvey et al.
Examiner: Schmidt	Group Art Unit: 1635

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-20 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-20 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 3-4

☐ Interview Summary, PTO-413

☒ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Action Summary

DETAILED ACTION

Oath/Declaration

1. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It was not executed in accordance with either 37 CFR 1.66 or 1.68.

2. The first line of the specification needs to be amended to read as follows: "This application claims the benefit of U.S. Provisional Application No. 60/053,509, filed July 23, 1997." (See MPEP 201.11)

Claim Rejections - 35 USC § 112

3. Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-20 contain the language "capable of" or "incapable of" which is indefinite for describing a latent characteristic of the primer, probe, sequence, etc., the scope of which is unclear. Definite language such as "which" or "is" is suggested.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 19-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Saunders et al.

Claim 19 is drawn to a method of preparing a sample containing RNA suitable for amplification comprising (1) providing a biological sample comprising unpurified RNA, (2) mixing the biological sample with a solution comprising a buffer at a pH of about 6.5 to about 8.5, at least about 150mM of a soluble salt, an effective amount of a non-ionic detergent sufficient to release RNA from the biological sample without causing viscosity due to the release of chromosomal DNA, and a solid support to which is joined an immobilized oligonucleotide comprising a nucleotide base sequence that forms a stable immobilized oligonucleotide:RNA hybridization complex, (3) separating the hybridization complex joined to the solid support from unhybridized sample components and (4) washing the hybridization complex with a solution having sufficient salt concentration to maintain the hybridization complex. Claim 20 specifies the biological sample as uncoagulated blood, plasma or bone marrow.

Saunders et al. teach methods of RNA extraction having an immobilization step from blood cells (see col. 5 and col. 6). Specifically, they teach isolation of blood cell mRNA in a

buffer of pH 7.2 comprising 75mM NaCl, 25mM Na2EDTA and 0.1% Sarcosyl, followed by precipitation of the nucleic acids and capture of the mRNA on a dT oligo column.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eskola et al., Kacian et al. (U.S. Patent 5,399,491), and Saunders et al. in view of Rowley et al., Morris et al., von Lindern et al, Goddard et al., Gruenwald et al., and Ohki et al.

Claim 1 is drawn to a method for detecting a fusion nucleic acid via (A) amplification of a first single-stranded fusion nucleic acid having a splice junction using a primer which hybridizes 3' to the splice junction site to produce a plurality of second nucleic acid strands complementary to a portion of the first strand having (1) a complementary splice junction site, (2) a first probe binding site 3' of the splice site, and (3) a second probe binding site 5' of the splice site and which overlaps or is 3' to a sequence complementary to the first primer binding site, and (B) hybridizing a probe to the first or second probe binding site for detection of the probe:target hybrid as an indication of the presence of the fusion nucleic acid in the sample. Dependent claims 2-8 further specify (1) the first single-stranded fusion nucleic acid is an mRNA, the first primer is a promoter-primer, the polymerase is an RNA polymerase, the first probe is the same sense as the mRNA (claim 2), (2) the first single-stranded fusion nucleic acid is a mRNA, the second nucleic acid strands are complementary RNA, the second primer or promoter-primer hybridizes to the second primer site 3' to both the complementary splice junction and the first probe binding site and amplification includes, RNA polymerase, DNA-directed DNA polymerase and RNA-directed DNA polymerase (claim 3), (3) the probe binds to the second probe binding site and does not hybridize with the first single-stranded nucleic acid (claim 4), (4) the fusion nucleic acid ia a bcr-abl fusion mRNA and the probe binds a bcr-derived nucleotide sequence in the second nucleic acid strand (claim 5), (5) the sample of claim 1 is first prepared via contacting a biological sample comprising the fusion nucleic acid with a solution comprising a buffer, about 150 mM to about 1M of a soluble salt, about 0.5% to about 1.5% (v/v/) of a non-ionic detergent and a solid support with an immobilized

oligonucleotide for separating the hybridized complex joined to the solid support from unhybridized sample components (claim 6), the fusion nucleic acid is mRNA (claim 7) and the nucleotide base sequence of the immobilized oligonucleotide comprises a poly-T sequence (claim 8).

Claim 9 is drawn to a method for detecting a fusion mRNA transcript produced as a result of a chromosomal translocation via (1) providing a sample containing a fusion mRNA transcript comprising a splice junction, (2) amplifying the fusion mRNA with a first primer which hybridizes to the fusion mRNA at a first primer binding site derived from a first chromosomal region and located 3' to the splice junction site with polymerase to produce a plurality of second nucleic acid strands complementary to a portion of the fusion mRNA containing the splice junction site which is (a) complementary to the splice junction site, (b) has a first probe binding site located 3' to and not overlapping the complementary splice site, and c) a second probe site located 5' to and not overlapping the complementary splice site, wherein the second probe site is derived from a third chromosomal region and overlaps or is 3' to the first primer binding site, (3) hybridizing the second nucleic acid strands with an oligo probe which hybridizes to the first or second probe binding site but does not hybridize to the fusion transcript, and (4) detecting the hybridization complex as an indication of the presence of the fusion transcript in the sample. Dependent claims 10-18 specify the following limitations: the amplifying step uses a first primer that is a promoter primer, an RNA polymerase and an oligonucleotide probe that binds to the first probe binding site (claim 10), the first probe binding site and the second probe binding site are derived from different

locations on the same chromosome in a eukaryotic cell and the fusion mRNA results from an intrachromosomal translocation (claim 11), the first probe binding site is derived from a different chromosome than the chromosome from which the second probe binding site is derived, and the fusion mRNA results from a translocation involving different chromosomes (claim 12) such as from the following human translocations: t(1'19), t(2;5), t(2;13), t(4;11), t(6;9), t(8;21), t(9;11), t(9;22), t(11;14), t(11;19), t(11;22), t(12;21), t(14;18) and t(15;17) (claim 13), or more specifically, t(9;22) and the oligonucleotide probe comprises a bcr-derived or abl-derived sequence (claim 14) and the following SEQ ID NOS are applicable: 1, 23, 26, and 27 (claim 15), the amplification is performed using an RNA polymerase, a DNA-directed DNA polymerase or an RNA-directed DNA polymerase and further uses a second primer or promoter primer to a sequence produced during the amplification step (claim 16), the polymerase activity is supplied by a reverse transcriptase (claim 17), and the method comprises an internal control transcript (claim 18).

Eskola et al. teach PCR methods for the detection of a bcr/abl gene translocations for applications for rapid clinical isolation of such gene translocations (see the abstract and pages 374 and page 377 in particular). They do not specifically teach the methods of RNA isolation, specific primers or other chromosomal translocations instantly claimed.

Saunders et al. in column 5 teach a method of RNA isolation from blood cells using a buffer comprising NaCl, NaEDTA and Sarkosyl (detergent) and subsequent isolation of Poly A+

RNA via passage over an oligo dT column. The RNA isolation was followed by reverse transcription (col. 6).

Kacian et al (U.S. Patent 5,399,491) teach methods for amplification of RNA for detection of target sequences (see col.3 and 4). They teach specific application of a primer having 89% homology to instant SEQ ID NO 23 because they teach T7 promoter primers. They also teach application of various DNA-directed DNA polymerase, RNA-directed DNA polymerase and reverse transcriptase (see col. 8). They do not specifically teach application of the method to detection of other such chromosomal translocations.

Rowley et al. teach methods for detection of the following gene translocations: (4;11) col 2, line 16; (9;11) col 2, line 19; (9;22) abstract; (11;14) col 23, line 7; (11;19) col 2, line 16; (11;22) col. 9, line 22; (14;18) col. 32, line 25. Rowley et al. do not teach (1;19), (2;5), (2;13), (6;9), (8;21), (12;21) or 15;17).

Morris et al. teach methods of detection of the translocation t(2:5) from a sample using hybridization of probes for amplification (see col. 2 and col. 5). They do not teach application to other such translocations.

Gruenwald et al.teach (1:19).

Von Lindern et al. teach (6;9).

Ohki et al. teach (8;21).

Goddard et al. teach (15;17).

It would have been prima facie obvious to one of ordinary skill in the art to identify known human chromosomal translocation or other such fusion genes via the method of RNA isolation taught by Saunders et al. followed by the amplification using primers to known translocation sequences (such as the brl/abl sequences taught by Kacien et al. or Eskola) because such amplification methods were known in the art as taught by Kacian et al. (US Patent 5,399,491) and Eskola. It would have been prima facie obvious to apply the instant method to identify other known chromosomal translocations in the art such as those taught by Rowley et al., Morris et al., von Lindern et al, Goddard et al., Gruenwald et al., and Ohki et al.

One of ordinary skill in the art would have been motivated to (1) substitute the method of isolation of mRNA from a biological sample such as blood taught by Saunders et al. for the kit taught by Eskola et al. p. 375, col. 1, "Extraction of RNA") since those techniques were known for specific column purification of mRNA, (2) to detect and amplify via hybridization of primer sequences to an RNA population a chromosomal translocation product RNA via a method taught by Eskola et al. and Kacian et al. (US Patent 5,399,491) because such amplification techniques were known in the art for detection of chromosomal translocations. One of ordinary skill in the art would have been motivated to detect via the above combination of methods mRNA having chromosomal translocation sequences such as those taught by Rowley et al., Morris et al., von Lindern et al, Goddard et al., Gruenwald et al. and Ohki et al. for the reasons taught by Eskola for rapid detection of such translocation products by clinical laboratories.

One of ordinary skill in the art would have had a reasonable expectation of success to isolate mRNA from biological samples as taught by Saunders et al., and further, detect known chromosomal translocation products known in the art as taught by Rowley et al., Morris et al., von Lindern et al, Goddard et al., Gruenwald et al. and Ohki et al. because isolation of RNA, reverse transcription and amplification of RNA having a known target sequence were well known in the art as exemplified by the methods of Eskola et al. and Kacian et al. (US Patent 5,399,491).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *George Elliott, Ph.D.* may be reached at (703) 308-4003. The examiner's primary, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

M. M. Schmidt
August 16, 1999

JOHN L. LeGUYADER
PRIMARY EXAMINER
GROUP 1800